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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,804	03/13/2007	Meilin Liu	IMCLON 3.3-005	1328

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EXAMINER	
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ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,804	LIU ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *14-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of claims 1-13 in the reply filed on 02/25/2008 is acknowledged.

Priority

2. This Application is a National Stage entry of the application PCT/US07/09583 filed on 03/21/2005 which claims priority to the provisional Applications 60/554555 and 60/624264. However, the Sequences 2, 4, 6, 8, 10, 12, 14, and 16, claimed in the PCT Application were not disclosed in the provisional Applications. Consequently, the priority benefit of the provisional application 60/554555 and 60/624264 has not been granted.

Status of the claims

3. Claims 1-41 are pending. Claims 14-41 are withdrawn as being drawn to non-elected inventions. Claims 1-13 are currently being examined.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-5 and 8-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to: an isolated human antibody or antibody fragment comprising one or more complementarity determining regions selected from the group consisting of SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16. The antibody or antibody fragment binds selectively to EGFR and might inhibit binding of EGFR to a ligand of EGFR or neutralizes EGFR. The antibody fragment is selected from the group consisting of a single chain antibody, an Fab, a single chain Fv, a diabody, and a triabody. Also claimed is conjugate of the antibody or antibody fragment to an anti-neoplastic agent, a target moiety or a reporter moiety.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the factor present in the claims is a partial structure in the form of specific complementary determining regions. The accepted state of the art with respect to antibodies shows that the antibody specificity is conferred by at least five if not the full complement of six CDRs (figure 3.8, paragraph 3.6, in chapter 3, Immunobiology, Janeway et al. eds., Garland publishing, New York, 2001, ISBN 081533642 X). Reduction to practice in effect provides the only evidence to corroborate conception (and therefore possession) of the invention.

With regard to claim 12, the conjugate of the antibody is missing one key element, the conjugation partner. There is no description of the possible conjugation partner so as to adequately describe the claim.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Therefore, only claims 6 and 7, which fully describe the antibody claimed described meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

6. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for an isolated antibody comprising **all** the six CDRs (3 CDRs of a heavy chain amino acid sequence **and** 3 CDRs of a light chain amino acid sequence) and which binds to EGRF, does not reasonably provide enablement for antibodies that have any of the above mentioned sequences missing or fragments of the antibodies and without the knowledge whether it binds to a specific antigen such as EGFR.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention

commensurate in scope with these claims. Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized In re Wands (858 F2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

This rejection encompasses two distinct issues, which will be addressed in turn: Enablement is not commensurate in scope with claims to make and use any isolated protein antibody that does not contains all six immunoglobulin variable domains CDRs from immunoglobulin heavy and light chains.

The specification discloses the IMC-11F8 antibody that binds specifically to the extracellular domain of EGFR receptor (p.12). The specification does not teach how to make and use any isolated protein mentioned above that lacks all six immunoglobulin variable domains CDRs from immunoglobulin heavy and light chains and has the properties of the IMC-11F8.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRS which provide the majority of the contact residues for the binding of the antibody to its target epitope. The

amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRS in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRS, may dramatically affect antigen-binding function as evidenced by Rudikoff et al. (Proc. Natl. Acad. Sci. USA 79: 1979, 1982), which teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Kobrin et al (J Immunology 146: 2017-2020, 1991) teach that a single amino acid substitution from aspartic acid to asparagine at residue 95 of the heavy chain variable region of a phosphocholine binding monoclonal antibody resulted in loss of antigen binding (see entire document, abstract, in particular). Barrios et al (J Molecular Recognition 17: 332-338, 2004) teach the length of the antibody heavy chain CDR3 is critical for antigen specific binding site (see abstract, in particular). Further, the length of the amino acid sequence that linked the CDRs of light and heavy chains (framework region) is important in maintaining their required conformation for binding and in vivo activity. Given the insufficient guidance and in vivo working examples, it is unpredictable which undisclosed isolate protein comprising only one CDR (claim 1) still binds specifically to EGFR ectodomain and has the properties

claimed. Accordingly, an undue amount of experimentation would be required to determine how to make and use the claimed invention with an antibody having less then 6 CDRs.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1 and 8-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Jakobovits et al. (U.S. Pat. No. 6,235,883).

Jakobovits et al. teach fully human contiguous heavy and light chain sequences spanning the complementarity determining regions monoclonal antibodies against human epidermal growth factor receptor (EGF-r). Amino acid sequences comprising heavy and light chain immunoglobulin molecules, particularly sequences corresponding to CDRs, specifically from CDR1 through CDR3 (abstract). In a preferred embodiment, the heavy chain variable region comprises the contiguous sequence from CDR1 through CDR3 as represented in Seq. Id. No. 35 (col. 9, lines 42-64). The seq. Id. No. 2 of the instant Application is comprised in Seq. Id. No. 35 of the Jakobovits et al. patent. Antibodies in accordance with the present invention are potent inhibitors of EGF and TGF-α binding to its receptor, EGF-r (col. 21, lines 4-13 and Example 5). Binding fragments include Fab, Fab', F $(ab')_2$, Fv, and single-chain antibodies (col. 17, line 65 to

col. 18, line 4). The antibody are labeled (i.e. conjugated) by incorporation of a detectable marker, e.g., by incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotinyl moieties that can be detected by marked avidin (e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). In certain situations, the label or marker can also be therapeutic (col. 18, lines 25-32).

Thus, the claims 1 and 8-13 are anticipated by Jakobovits et al.

9. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Siegel et al. (WO/2004/005890, 01-2004).

Siegel et al. describes the amino acid sequence of the heavy chain of an antibody which comprises the sequence referred to as Seq. Id. No. 4 of the instant Application (Seq. Id. No. 69, p. 21, lines 17-1 8, Figure 19p).

Therefore claim 1 is anticipated by Siegel et al.

10. Claims 1 and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Deo et al. ((WO/03/064606, 08/2003).

Deo et al. teach human monoclonal antibodies and single-chain Fv to prostate specific membrane antigen comprising the sequences of SEQ. ID. Nos. : 10 and 12 of the instant Application (Seq. Id. Nos. 37, 39, 40, 40, 42 and 43; claims 2 and 3, p.2, lines 16-32). Also disclosed are immunoconjugates with other therapeutic agents.

Therefore the claims 1 and 11-13 are anticipated by Deo et al.

Conclusion

11. None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Manjunath N. Rao, /
Supervisory Patent Examiner, Art Unit 1647